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(71) Applicant: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors: **FLOHR, Alexander**; 142 St. Galler-Ring, CH-4054 Basle (CH). **JAKOB-ROETNE, Roland**; Oberer Baselblick 37, 79595 Inzlingen (DE). **NORCROSS, Roger, David**; Alte Saline 20, CH-4310 Rheinfelden (CH). **RIEMER, Claus**; Optizstrasse 5, 79110 Freiburg (DE).

(74) Agent: **POPPE, Regina**; Grenzacherstrasse 124, CH-4070 Basel (CH).

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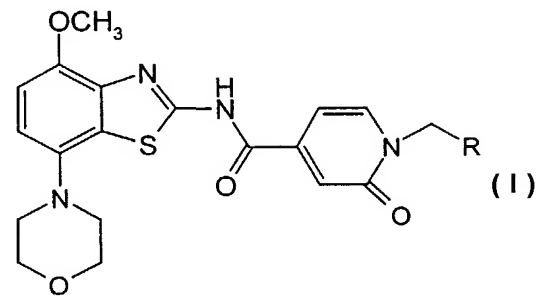
(54) Title: BENZOTHIAZOLE DERIVATIVES AS ADENOSINE RECEPTOR LIGANDS

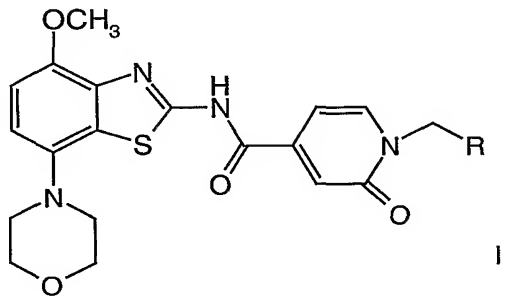


(I)

(57) Abstract: The present invention relates to compounds of the general formula (I): wherein R is phenyl, pyridin-2-yl, -C(O)-O-lower alkyl, -C(O)-lower alkyl, -C(O)-morpholinyl, -C(O)-NR'$_2$,-(CH$_2$)$_N$-NR'$_2$or -(CH$_2$)$_N$-O-lower alkyl and R' may be hydrogen or lower alkyl; and to pharmaceutically acceptable acid addition salts thereof. The compounds disclosed in this application have a good affinity to the A_{2A} receptor and therefore they may be used in the control or prevention of illnesses based on the modulation of the adenosine system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents for disorders such as coronary artery disease and heart failure.

BENZOTHIAZOLE DERIVATIVES AS ADENOSINE RECEPTOR LIGANDS

The present invention relates to compounds of the general formula



I

wherein

R is phenyl, pyridin-2-yl, -C(O)-O-lower alkyl, C(O)-lower alkyl, -C(O)-morpholinyl, -C(O)-NR'$_2$, -$(CH_2)_n$-NR'$_2$ or -$(CH_2)_n$-O-lower alkyl and R' may be hydrogen or lower alkyl;
and to pharmaceutically acceptable acid addition salts thereof.

It has surprisingly been found that the compounds of general formula I are adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A_{2A}-receptor and a high selectivity to the A_1- and A_3 receptors and, in addition, they have a good water solubility.

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors. The potential of adenosine receptors as drug targets was first reviewed in 1982. Adenosine is related both structurally and metabolically to the bioactive nucleotides adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP) and cyclic adenosine monophosphate (cAMP); to the biochemical methylating agent S-adenosyl-L-methione (SAM); and structurally to the coenzymes NAD, FAD and coenzym A; and to RNA. Together adenosine and these related compounds are important in the regulation of many aspects of cellular metabolism and in the modulation of different central nervous system activities.

The receptores for adenosine have been classified as A_1, A_{2A}, A_{2B} and A_3 receptors, belonging to the family of G protein-coupled receptors. Activation of adenosine receptors by adenosine initiates signal transduction mechanism. These mechanisms are dependent on the receptor associated G protein. Each of the adenosine receptor subtyps has been classically characterised by the adenylate cyclase effector system, which utilises cAMP as a second messenger. The A_1 and A_3 receptors, coupled with G_i proteins inhibit adenylate cyclase, leading to a decrease in cellular cAMP levels, while A_{2A} and A_{2B} receptors couple to G_s proteins and activate adenylate cyclase, leading to an increase in cellular cAMP levels. It is known that the A_1 receptor system include the activation of phospholipase C and modulation of both potassium and calcium ion channels. The A_3 subtype, in addition to its association with adenylate cyclase, also stimulates phospholipase C and so activates calcium ion channels.

The A_1 receptor (326-328 amino acids) was cloned from various species (canine, human, rat, dog, chick, bovine, guinea-pig) with 90–95 % sequence identify among the mammalian species. The A_{2A} receptor (409-412 amino acids) was cloned from canine, rat, human, guinea pig and mouse. The A_{2B} receptor (332 amino acids) was cloned from human and mouse with 45 % homology of human A_{2B} with human A_1 and A_{2A} receptors. The A_3 receptor (317-320 amino acids) was cloned from human, rat, dog, rabbit and sheep.

The A_1 and A_{2A} receptor subtypes are proposed to play complementary roles in adenosine's regulation of the energy supply. Adenosine, which is a metabolic product of ATP, diffuses from the cell and acts locally to activate adenosine receptors to decrease the oxygen demand (A_1) or increase the oxygen supply (A_{2A}) and so reinstate the balance of energy supply: demand within the tissue. The actions of both subtyps is to increase the amount of available oxygen to tissue and to protect cells against damage caused by a short term imbalance of oxygen. One of the important functions of endogenous adenosine is preventing damage during traumas such as hypoxia, ischaemia, hypotension and seizure activity.

Furthermore, it is known that the binding of the adenosine receptor agonist to mast cells expressing the rat A_3 receptor resulted in increased inositol triphosphate and intracellular calcium concentrations, which potentiated antigen induced secretion of inflammatory mediators. Therefore, the A_3 receptor plays a role in mediating asthmatic attacks and other allergic responses.

Adenosine is a neuromodulator, able to modulate many aspects of physiological brain function. Endogenous adenosine, a central link between energy metabolism and neuronal activity, varies according to behavioural state and (patho)physiological conditions. Under conditions of increased demand and decreased availability of energy

(such as hypoxia, hypoglycemia, and/or excessive neuronal activity), adenosine provides a powerful protective fedback mechanism. Interacting with adenosine receptors represents a promising target for therapeutic intervention in a number of neurological and psychiatric diseases such as epilepsy, sleep, movement disorders (Parkinson or Huntington's disease), Alzheimer's disease, depression, schizophrenia, or addiction An increase in neurotransmitter release follows traumas such as hypoxia, ischaemia and seizures. These neurotransmitters are ultimately responsible for neural degeneration and neural death, which causes brain damage or death of the individual. The adenosine A_1 agonists which mimic the central inhibitory effects of adenosine may therefore be useful as neuroprotective agents. Adenosine has been proposed as an endogenous anticonvulsant agent, inhibiting glutamate release from excitory neurons and inhibiting neuronal firing. Adenosine agonists therefore may be used as antiepileptic agents. Adenosine antagonists stimulate the activity of the CNS and have proven to be effective as cognition enhancers. Selective A_{2a} antagonists have therapeutic potential in the treatment of various forms of dementia, for example in Alzheimer's disease, and of neurodegenerative disorders, e.g. stroke. Adenosine A_{2a} receptor antagonists modulate the activity of striatal GABAergic neurons and regulate smooth and well-coordinated movements, thus offering a potential therapy for Parkinsonian symptoms. Adenosine is also implicated in a number of physiological processes involved in sedation, hypnosis, schizophrenia, anxiety, pain, respiration, depression, and drug addiction (amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids). Drugs acting at adenosine receptors therefore have therapeutic potential as sedatives, muscle relaxants, antipsychotics, anxiolytics, analgesics, respiratory stimulants, antidepressants, and to treat drug abuse. They may also be used in the treatment of ADHD (attention deficit hyper-activity disorder).

An important role for adenosine in the cardiovascular system is as a cardioprotective agent. Levels of endogenous adenosine increase in response to ischaemia and hypoxia, and protect cardiac tissue during and after trauma (preconditioning). By acting at the A_1 receptor, adenosine A_1 agonists may protect against the injury caused by myocardial ischemia and reperfusion. The modulating influence of A_{2a} receptors on adrenergic function may have implications for a variety of disorders such as coronary artery disease and heart failure. A_{2a} antagonists may be of therapeutic benefit in situations in which an enhanced antiadrenergic response is desirable, such as during acute myocardial ischemia. Selective antagonists at A_{2a} receptors may also enhance the effectiveness of adenosine in terminating supraventricula arrhytmias.

Adenosine modulates many aspects of renal function, including renin release, glomerular filtration rate and renal blood flow. Compounds which antagonise the renal affects of adenosine have potential as renal protective agents. Furthermore, adenosine A_3

and/or A_{2B} antagonists may be useful in the treatment of asthma and other allergic responses or and in the treament of diabetes mellitus and obesity.

Numerous documents describe the current knowledge on adenosine receptors, for example the following publications:

Bioorganic & Medicinal Chemistry, 6, (1998), 619-641,
Bioorganic & Medicinal Chemistry, 6, (1998), 707-719,
J. Med. Chem., (1998), 41, 2835-2845,
J. Med. Chem., (1998), 41, 3186-3201,
J. Med. Chem., (1998), 41, 2126-2133,
J. Med. Chem., (1999), 42, 706-721,
J. Med. Chem., (1996), 39, 1164-1171,
Arch. Pharm. Med. Chem., 332, 39-41, (1999),
Am. J. Physiol., 276, H1113-1116, (1999) or
Naunyn Schmied, Arch. Pharmacol. 362, 375-381, (2000).

Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases, related to the adenosine A_2 receptor, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses based on the modulation of the adenosine system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents for disorders such as coronary artery disease and heart failure. The most preferred indications in accordance with the present invention are those, which base on the A_{2A} receptor antagonistic activity and which include disorders of the central nervous system, for example the treatment or prevention of Alzheimer's disease, certain depressive disorders, drug addiction, neuroprotection and Parkinson's disease as well as ADHD.

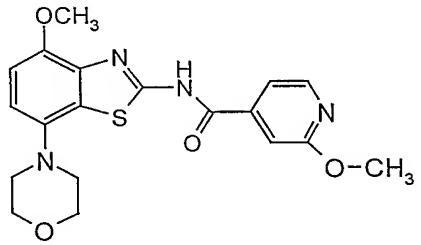
As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1 - 4 carbon atoms.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds of the present application are those, wherein R is phenyl, pyridin-2-yl, -C(O)-O-CH_2CH_3, -C(O)-CH_2CH_3, -C(O)-morpholinyl or -C(O)-$N(CH_3)_2$, which are the folowing:
1-benzyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
[4-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl-carbamoyl)-2-oxo-2H-pyridin-1-yl]-acetic acid ethyl ester,
2-oxo-1-(2-oxo-butyl)-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
2-oxo-1-pyridin-2-yl-methyl-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
1-(2-morpholin-4-yl-2-oxo-ethyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide or
1-dimethylcarbamoylmethyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

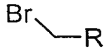
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which processes comprise

a) reacting a compound of formula



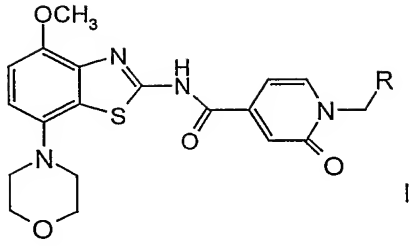
(6)

with a compound of formula



(7)

to a compound of formula

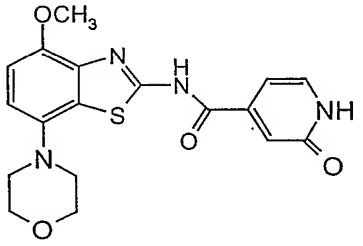


I

wherein R is phenyl, pyridyl, -C(O)O-lower alkyl or –C(O)-lower alkyl,

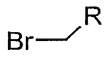
or

b) reacting a compound of formula

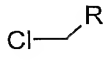


(8)

with a compound of formula

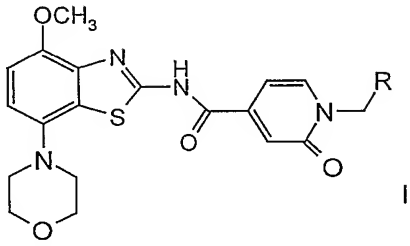


(7) or



(9)

to a compound of formula



I

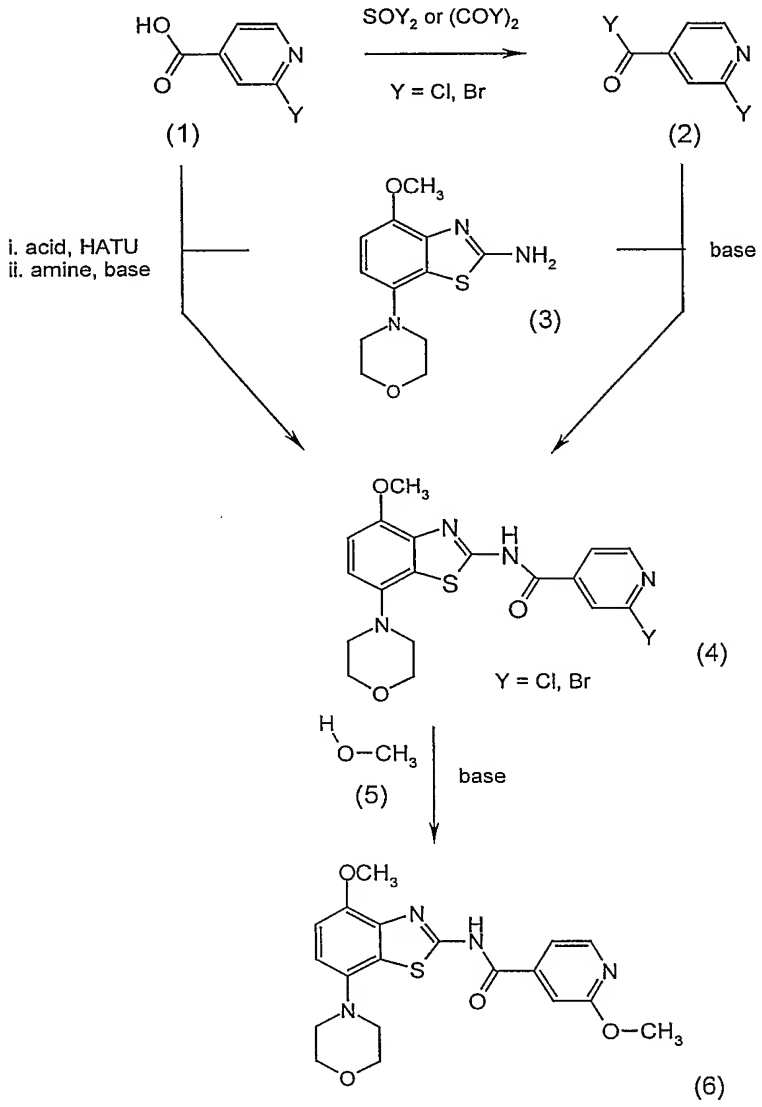
wherein R is –C(O)-morpholinyl, -$(CH_2)_n$-O-lower alkyl, -$(CH_2)_n$NR'$_2$ or –C(O)NR'$_2$, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

Preparation of compounds of formula I wherein R is phenyl, pyridyl, -C(O)O-lower alkyl or C(O)-lower alkyl

One method of preparation of compounds of formula I, wherein R is phenyl, pyridyl, -C(O)O-lower alkyl or C(O)-lower alkyl, is from a 2-methoxy-isonicotinamide intermediate of formula (6), as shown in reaction Schemes 1 and 2 below.

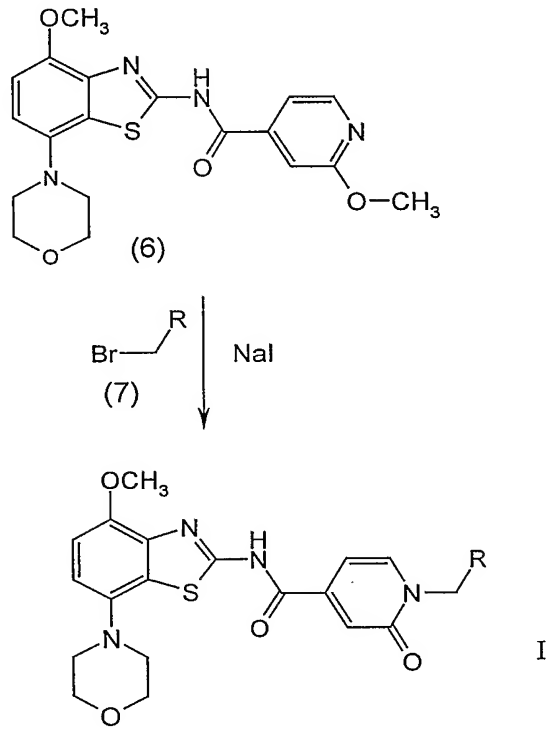
Scheme 1



In this scheme the following abbreviation has been used:

HATU O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

Scheme 2



wherein R is phenyl, pyridyl, -C(O)O-lower alkyl or C(O)-lower alkyl.

Preparation of compounds of formula (2)

The starting 2-chloroisonicotinic acid or 2-bromoisonicotinic acid of formula (1) may be obtained commercially, for example from Maybridge Chemicals, or may be prepared according to methods well known in the art.

The 2-haloisonicotinic acid of formula (1) may be converted to the corresponding acyl halide derivative of formula (2) by reacting a compound of formula (1) with an excess of a halogenating agent, such as oxalyl chloride or oxalyl bromide, or thionyl chloride or thionyl bromide, using a catalyst such as N,N-dimethylformamide or pyridine, in an organic solvent, prefereably dichloromethane or dichloroethane, at room temperature for about 2-16 hours, preferably 16 hours. The product of formula (2) is isolated by conventional means, and preferably reacted in the next step without further purification.

Preparation of compounds of formula (4)

The starting 2-amino-benzothiazole compound of formula (3) may be prepared according to methods disclosed in EP 00113219.0.

The compounds of formula (4) are prepared by treating the 2-amino-benzothiazole compounds of formula (3) with a slight excess of the acyl halide compounds of formula (2) in a non-protic organic solvent, preferably a mixture of dichloromethane and tetrahydrofuran, containing a base, preferably N-ethyldiisopropylamine or triethylamine, at room temperature for 2-24 hours, preferably 24 hours. The product of formula (4) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Alternative preparation of compounds of formula (4)

The compounds of formula (4) may also be prepared directly from compounds of formula (1). In this method, the compound of formula (1) is treated with a stoichiometric equivalent of a peptide-coupling reagent, preferably O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), in an ethereal solvent, preferably tetrahydrofuran, containing a base, preferably N-ethyldiisopropylamine, at room temperature for 30-90 minutes. This mixture is then treated with a 2-amino-benzothiazole compound of formula (3) in a solvent mixture, preferably a mixture of tetrahydrofuran, dioxane and N,N-dimethylformamide, at room temperature for 16-24 hours, preferably 24 hours. The product of formula (4) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula (6)

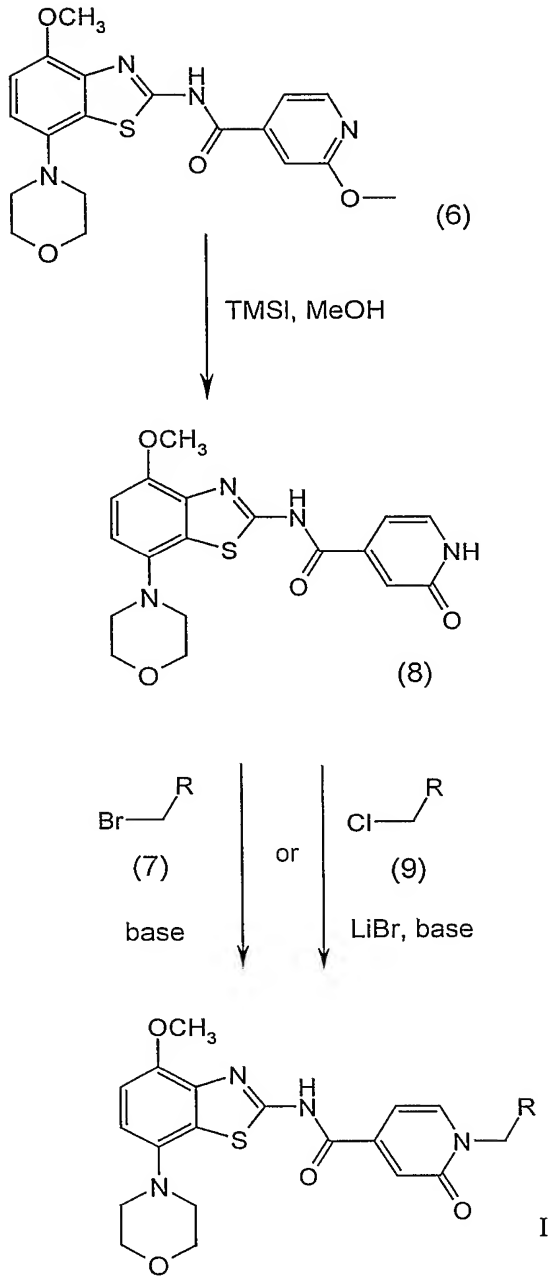
One method of preparation of a compound of formula (6) is by treatment of a compound of formula (4) with an excess of methanol, together with a metal-hydride base, preferably sodium hydride or potassium hydride. These reactions may be carried out in an ethereal solvent such as such as dioxane, tetrahydrofuran or 1,2-dimethoxyethane, preferably dioxane, optionally containing a co-solvent such as N,N-dimethylformamide, at a temperature between room temperature and the reflux temperature of the solvent, preferably about 100 °C, for 2-72 hours, preferably 16 hours. The product of formula (6) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

The compound of formula (6) is treated with an excess of an alkyl bromide of formula (7), which may be commercially available or may be prepared by methods well known in the art, according to the procedure of *Synthetic Commun.* 1999, *29*, 4051-4059. These reactions may be carried out in a polar organic solvent such as acetonitrile or *N,N*-dimethylformamide, preferably *N,N*-dimethylformamide, at an elevated temperature, preferably the reflux temperature of the solvent used, for 2-18 hours, preferably 16 hours. The product of formula I, where R is phenyl, pyridyl, -C(O)O-lower alkyl or C(O)-lower alkyl, is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula I, wherein R is –C(O)-morpholinyl, -$(CH_2)_n$-NR'$_2$, -$(CH_2)_n$-O-lower alkyl or C(O)NR'$_2$

One method of preparation of compounds of formula I, wherein R is –C(O)-morpholinyl, -$(CH_2)_n$-NR'$_2$, -$(CH_2)_n$-O-lower alkyl or C(O)NR'$_2$, is from a 2-oxo-1,2-dihydro-pyridine-4-carboxylic acid amide intermediate of formula (8), the preparation of which is shown in reaction scheme 3 below.

Scheme 3



wherein R is –C(O)-morpholinyl, -$(CH_2)_n$-NR'$_2$, -$(CH_2)_n$-O-lower alkyl, or-C(O)NR'$_2$ and TMSI is iodotrimethylsilane.

Preparation of compounds of formula (8)

The compound of formula (6) is treated with an excess of iodotrimethylsilane in a halogenated organic solvent, preferably chloroform, at room temperature or above, preferably at the reflux temperature of the solvent, for 2-16 hours, preferably about 8 hours. The reaction mixture is then treated with an alcohol, preferably methanol, at room

temperature or above, preferably at the reflux temperature of the solvent mixture, for 2-18 hours, preferably about 16 hours. The product of formula (8) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula I, wherein R is –C(O)-morpholinyl, $-(CH_2)_n-NR'_2$, $-(CH_2)_n$-O-lower alkyl or $-C(O)NR'_2$

The compound of formula (8) is treated with an excess of an alkyl bromide of formula (7) or an alkyl chloride of formula (9), which may be commercially available or may be prepared by methods well known in the art. In the case where an alkyl chloride of formula (9) is used, the reaction is performed in the presence of a stoichiometric equivalent of lithium bromide. These reactions may be carried out in a polar organic solvent such as dioxane or *N,N*-dimethylformamide, preferably a mixture of *N,N*-dimethylformamide and dioxane, at a temperature between room temperature and the reflux temperature of the solvent mixture used, for 2-18 hours, preferably 16 hours. The product of formula I is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the Preparations and examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used.

Salts of compounds of formula I

The compounds of formula I may be basic, for example in cases where the residue R contains a basic group such as an aliphatic or aromatic amine moiety. In such cases the compounds of formula I may be converted to a corresponding acid addition salt.

The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids suchas acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the

free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it could be demonstrated that the compounds of the present invention are adenosine receptor ligands and possess a high affinity towards the adenosine A_{2A} receptor and a good selectivity towards A_1 receptor.

The compounds were investigated in accordance with the tests given hereinafter.

Human adenosine A_1 receptor

The human adenosine A_1 receptor was recombinantly expressed in chinese hamster ovary (CHO) cells using the semliki forest virus expression system. Cells were harvested, washed twice by centrifugation, homogenised and again washed by centrifugation. The final washed membrane pellet was suspended in a Tris (50 mM) buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 10 mM $MgCl_2$ (pH 7.4) (buffer A). The [^{3}H]-DPCPX (([propyl-^{3}H]8-cyclopentyl-1,3-dipropyxanthine); 0.6 nM) binding assay was carried out in 96-well plates in the presence of 2.5 µg of membrane protein, 0.5 mg of Ysi-poly-l-lysine SPA beads and 0.1 U adenosine deaminase in a final volume of 200 µl of buffer A. Non-specific binding was defined using xanthine amine congener (XAC; 2 µM). Compounds were tested at 10 concentrations from 10 µM - 0.3 nM. All assays were conducted in duplicate and repeated at least two times. Assay plates were incubated for 1 hour at room temperature before centrifugation and then bound ligand determined using a Packard Topcount scintillation counter. IC_{50} values were calculated using a non-linear curve fitting program and Ki values calculated using the Cheng-Prussoff equation.

Human adenosine A_{2A} receptor

The human adenosine A_{2A} receptor was recombinantly expressed in chinese hamster ovary (CHO) cells using the semliki forest virus expression system. Cells were harvested, washed twice by centrifugation, homogenised and again washed by centrifugation. The final washed membrane pellet was suspended in a Tris (50 mM) buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 10 mM $MgCl_2$ (pH 7.4) (buffer A). The [^{3}H]-SCH-

58261 (Dionisotti et al., 1997, Br J Pharmacol 121, 353; 1nM) binding assay was carried out in 96-well plates in the presence of 2.5 μg of membrane protein, 0.5 mg of Ysi-poly-l-lysine SPA beads and 0.1 U adenosine deaminase in a final volume of 200 μl of buffer A. Non-specific binding was defined using xanthine amine congener (XAC; 2 μM). Compounds were tested at 10 concentrations from 10 μM - 0.3 nM. All assays were conducted in duplicate and repeated at least two times. Assay plates were incubated for 1hour at room temperature before centrifugation and then bound ligand determined using a Packard Topcount scintillation counter. IC_{50} values were calculated using a non-linear curve fitting program and Ki values calculated using the Cheng-Prussoff equation.

It has been shown that compounds of formula I have a good affinity to the A_{2A} receptor and a high selectivity toward the A_1 receptor. The preferred compounds show a pKi > 7.2, as described in the table below:

Example No.	hA_1(pKi)	hA_2 (pKi)
1	5.90	8.67
2	5.18	8.19
3	5.18	8.24
4	5.18	8.10
5	5.18	7.23
6	5.18	7.30

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid

polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on the adenosine receptor antagonistic activity, such as Alzheimer's disease, Parkinson's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents and for the production of corresponding medicaments.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders, neuroprotection and Parkinson's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

The following preparation and examples illustrate the invention but are not intended to limit its scope.

Example 1

1-Benzyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

To a stirred solution of 85 mg (0.21 mmol) 2-methoxy-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-isonicotinamide in 2 ml acetonitrile were added 73 mg (0.43 mmol) sodium iodide and 0.05 ml (0.43 mmol) benzyl bromide. The mixture was heated at reflux for 16 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, and washed sequentially with water and saturated brine. The organic phase was then dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (2/1 EtOAc/toluene) afforded 32 mg (32 %) 1-benzyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide as a yellow crystalline solid. ES-MS m/e (%): 499 ($M+Na^+$, 14), 477 ($M+H^+$, 100).

In an analogous manner there were obtained:

Example 2

[4-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-ylcarbamoyl)-2-oxo-2H-pyridin-1-yl]-acetic acid ethyl ester

From 2-methoxy-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-isonicotinamide with sodium iodide and ethyl bromoacetate in DMF. ES-MS m/e (%): 495 ($M+Na^+$, 25), 473 ($M+H^+$, 100).

Example 3

2-Oxo-1-(2-oxo-butyl)-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

From 2-methoxy-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-isonicotinamide with sodium iodide and 1-bromo-2-butanone in DMF. ES-MS m/e (%): 479 ($M+Na^+$, 32), 457 ($M+H^+$, 100).

Example 4

2-Oxo-1-pyridin-2-ylmethyl-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

From 2-methoxy-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-isonicotinamide with sodium iodide and 2-(bromoethyl)pyridine hydrobromide in DMF. ES-MS m/e (%): 500 ($M+Na^+$, 30), 478 ($M+H^+$, 100).

Example 5

1-(2-Morpholin-4-yl-2-oxo-ethyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

To a stirred solution of 200 mg (0.52 mmol) 2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide in 1 ml DMF and 4 ml 1,2-dimethoxyethane was added 44 mg (1.04 mmol) sodium hydride (60% dispersion in mineral oil). After stirring for 15 min at room temperature, 90 mg (1.04 mmol) lithium bromide was added and stirring continued for a further 15 min. 95 mg (0.58 mmol) 4-(2-chloroacetyl)morpholine was then added and the mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with ethyl acetate, and washed sequentially with 0.5 M hydrochloric acid, saturated sodium bicarbonate solution and saturated brine. The combined aqueous phases were filtered, and the filter cake washed with ether, then resuspended in toluene and concentrated *in vacuo*. Flash chromatography (MeOH/CH2Cl2) followed by trituration in ethyl acetate afforded 83 mg (31 %) 1-(2-morpholin-4-yl-2-oxo-ethyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide as a yellow crystalline solid. ES-MS m/e (%): 536 ($M+Na^+$, 25), 514 ($M+H^+$, 100).

In an analogous manner there were obtained:

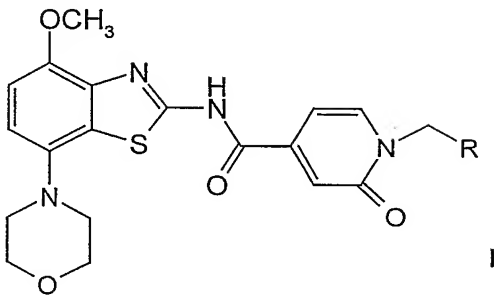
Example 6

1-Dimethylcarbamoylmethyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

From 2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide with sodium hydride, lithium bromide and 2-chloro-*N*,*N*-dimethylacetamide in 1,2-dimethoxyethane and DMF. ES-MS m/e (%): 494 ($M+Na^+$, 22), 472 ($M+H^+$, 100).

Claims

1. Compounds of the general formula



I

wherein

R is phenyl, pyridin-2-yl, -C(O)-O-lower alkyl, C(O)-lower alkyl, -C(O)-morpholinyl, -C(O)-NR'$_2$, -$(CH_2)_n$-NR'$_2$ or -$(CH_2)_n$-O-lower alkyl and R' may be hydrogen or lower alkyl;
and to pharmaceutically acceptable acid addition salts thereof.

2. Compounds of formula I in accordance with claim 1, wherein R is phenyl.

3. Compounds of formula I in accordance with claim 2, wherein the compound is 1-benzyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

4. Compounds in accordance with claim 1, wherein R is –C(O)O-lower alkyl.

5. Compounds in accordance with claim 4, wherein the compound is [4-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylcarbamoyl)-2-oxo-2H-pyridin-1-yl]-acetic acid ethyl ester.

6. Compounds in accordance with claim 1, wherein R is –C(O)-lower alkyl.

7. Compounds in accordance with claim 6, wherein the compound is 2-oxo-1-(2-oxo-butyl)-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

8. Compounds in accordance with claim 1, wherein R is pyridinyl.

9. Compounds in accordance with claim 8, wherein the compound is 2-oxo-1-pyridin-2-yl-methyl-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

10. Compounds in accordance with claim 1, wherein R is –C(O)-morpholinyl.

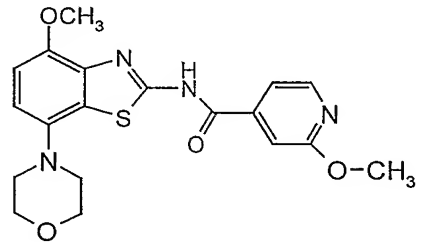
11. Compounds in accordance with claim 10, wherein the compound is 1-(2-morpholin-4-yl-2-oxo-ethyl)-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

12. Compounds in accordance with claim 1, wherein R is –C(O)-NR'$_2$.

13. Compounds in accordance with claim 12, wherein the compound is 1-dimethylcarbamoylmethyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

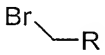
14. A process for preparing a compound of formula I as defined in claims 1 - 13, which processes comprise

a) reacting a compound of formula



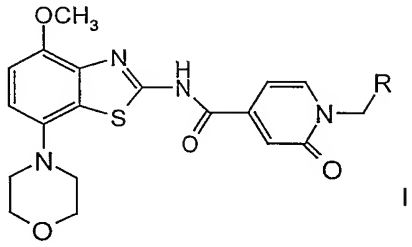
(6)

with a compound of formula



(7)

to a compound of formula



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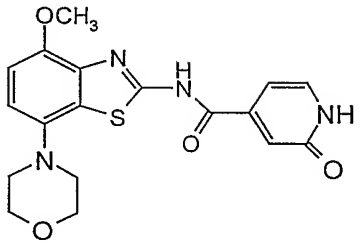
wherein R is phenyl, pyridyl, -C(O)O-lower alkyl or –C(O)-lower alkyl,

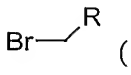
or

b) reacting a compound of formula

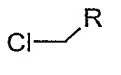


(8)

with a compound of formula

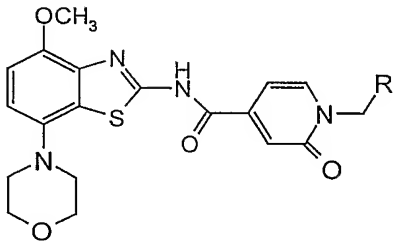


(7) or



(9)

to a compound of formula



I

wherein R is –C(O)-morpholinyl, -$(CH_2)_n$-O-lower alkyl, -$(CH_2)_n$NR'$_2$ or –C(O)NR'$_2$, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

15. A compound according to any one of claims 1 to 13, whenever prepared by a process as claimed in claim 14 or by an equivalent method.

16. A medicament containing one or more compounds as claimed in any one of claims 1 to 13 and pharmaceutically acceptable excipients.

17. A medicament according to claim 16 for the treatment of diseases related to the adenosine receptor.

18. The use of a compound in any one of claims 1 to 13 for the treatment of diseases.

19. The use of a compound in any one of claims 1 to 13 for the manufacture of corresponding medicaments for the treatment of diseases related to the adenosine A_{2A} receptor.

20. The invention as hereinbefore described.

***

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/12543

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4412 C07D417/12 A61P25/16 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 97786 A (HOFFMANN LA ROCHE) 27 December 2001 (2001-12-27) claims 1,19,29	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2003	29/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/12543

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20

The scope of claim 20 "The invention as hereinbefore described" is either merely a repetition of claims 1-19 in which case it is superfluous or a fully unclear reference to the description (Art 6 PCT). In either case it has not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/12543

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0197786 A	27-12-2001	AU 8181701 A	02-01-2002
		WO 0197786 A2	27-12-2001
		US 2002045615 A1	18-04-2002